UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/418,095	10/14/1999	JOHN A. COPLAND III	UTMB/GAL:239	8391

7590 10/17/2003

Fulbright & Jaworski
600 Congress Avenue
Suite 2400
Austin, TX 78701

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	21

DATE MAILED: 10/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/418,095	COPLAND III ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 7/28/2003 in Paper No. 20 has been entered.

Claims 1-46 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 15-16, 27-28, 33-35, 39-42 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) for the same reasons already set forth in the previous Office Action in Paper No. 19 (pages 3-4).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related

thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

The teachings of Urban et al. meet every limitation of the instant claims, and therefore the reference anticipates the presently claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in amendment filed on 7/28/2003 in Paper No. 20 (pages 3-6) have been fully considered, but they are respectfully not found persuasive.

(1) Applicants argue that Urban does not teach the use of chemotherapeutic drugs or radiation in combination with thiazolidinedione, and that Urban fails to enable any method that uses a thiazolidinedione in combination with chemotherapeutic drugs or radiation. Applicants further argue that Urban does not provide a single example of a combination therapy, and that the therapeutic effects of a thiazolidinedione compound in combination with other therapy in treating cancerous cells was unpredictable as believed by Examiner in an Office Action dated 8/16/2000 at page 5.

Urban clearly teach the essential concept of using troglitazone (as well as related thiazolidinedione compounds such as pioglitazone and BRL49653) therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery for the treatment of cancer (col. 24, lines 17-27). According to Webster's Dictionary, the term "conjunction" means union or concurrence (taking place at the same time or accompanying) of events. Therefore, Urban et al. anticipate the instant claimed invention.

With respect to the unpredictability of obtaining therapeutic effects for the use of a thiazolidinedione in combination with other therapy in treating cancerous cells, it is unclear which unpredictable factors are involved in cancer treatment or killing cancer cells via the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery. Chemotherapeutic agents, radiation or surgery were routinely used in cancer treatment at the effective filing date of the present application as evidenced by the teachings of Medenica et al., Jin et al. and Roth et al., for examples. In addition to the teachings of Urban et al. on the use of troglitazone and related thiazolidinedione compounds to kill transformed cell lines and even with human breast cancer MCF-7 cells that do not express PPARγ (see examples 5 & 6), at the effective filing date of the present application Mueller et al. (Mol. Cell 1:465-470, 1998; Cited previously) demonstrated that troglitazone or pioglitazone decreases the growth of human breast cancer 21PT cells; Brockman et al. (Gastroenterology 115:1049-1055, 1998; Cited previously) showed that BRL 49653 or rosiglitazone inhibits the growth of human colon cancer cells derived from various cell lines HCA-7, HCT-116, HCT-15 and HCT-15-G25; Elstner et al. (Proc. Natl. Acad. Sci. USA 95:8806-8811, 1998; Cited previously) disclosed clonal proliferation of human breast cancer cells derived from cell lines MCF7, T47D, MDA-MB-231 were inhibited by troglitazone (TGZ) in a concentration-dependent manner, and that this inhibition was further enhanced with the combination of TGZ and all-*trans*-retinoic acid (ATRA) which is an anti-neoplastic chemotherapeutic agent; Kubota et al. (Cancer Res. 58:3344-3352, 1998; Cited previously) taught that troglitazone and other PPAR-gamma ligands

including BRL49653 and others have anti-proliferative effects on the human PC-3 prostate cancer cells; and Tontonoz et al. (Proc. Natl. Acad. Sci. 94:237-241, 1997; IDS) disclosed that thiazolidinedione compounds such as pioglitazone, troglitazone and BRL49653 (rosiglitazone) can induce terminal differentiation of human liposarcoma cells *in vitro*, and that thiazolidinedione-induced differentiation of liposarcoma cells is accompanied by cell cycle growth arrest, which is in effect inhibiting liposarcoma cell growth. It is further noted that the enablement issue that was raised by the Examiner in the first Office Action dated 8/16/2000 in Paper No. 5 was withdrawn upon further consideration of the entirety of the prior art at the effective filing date of the present application. Additionally, under legal standards there is no requirement that Urban has to provide an example of a combination therapy to show its enablement, particularly in light of the totality of the prior art as discussed above.

(2) Applicants argue that Urban does not indicate in any way that a combination therapy would result in a therapy with a lowered toxicity (e.g., the present specification shows that a reduction in the dose of 5-FU by a factor of 100, page 57, lines 25-28 and Fig. 5) still achieves therapy, which would not have been known or predicted from the disclosure of Urban et al. alone or in combination with teachings of the prior art).

It is noted that the above rejection is a 102 (e) rejection, and therefore a reduction in the dose of 5-FU by a factor of 100 in a combinatorial therapy with 5μM

troglitazone in cultured SAOS-2 cells is irrelevant. Moreover, none of the claims recites the use of 5-FU in combination with 5μM troglitazone in cultured SAOS-2 cells.

(3) Applicants further argue even if one were to construe the words of Urban et al. as enabling, Urban et al. speak only to a genus of chemotherapeutic agents. Reference to a genus of chemotherapeutic agents can not anticipate the species of chemotherapeutic agents as set forth, at least, in claims 17 to 24 of the present invention.

Please note that claims 17 to 24 were not rejected under 35 U.S.C. 102(e) as being anticipated by Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997), only claims 1-10, 15-16, 27-28, 33-35, 39-42 and 46.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 16-25, 28-29 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Medenica et al. (U.S. Patent No. 5,736,129) for the same reasons already set forth in the previous Office Action in Paper No. 19 (pages 6-9).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor

growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

Urban et al. do not teach explicitly the types of chemotherapeutic drugs utilized in combination with the troglitazone therapy or the recited route of administration (e.g., regionally, intravenously, percutaneoulsy, perfusion) or resecting any tumor.

However at the effective filing date of the present application, different types of chemotherapeutic drugs, different routes of administering drugs as well as resecting tumors have been utilized in cancer treatment. Medenica et al. teach the use a multidrug chemotherapeutic regimen for cancer treatment in a patient. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-

FU, a corticosteroid hormone such as prednisone as well as chlorethel-methyl-cycloexyl-nitrosourea (See col. 6-10; and col. 22, lines 18-19). Medenica et al. specifically teach that it is known that a chemotherapeutic treatment regimen utilizing several drugs may be more effective than the best single drug, particularly a degree of **potentiation** exists between the agents in their efficacy against tumor cells to a greater extent than normal cells (col. 2; lines 42-55), and that the multidrug regimen has low toxicity insofar as ineffective chemotherapeutic agents are eliminated from the regimen (col. 5, lines 35-38). Medenica et al. also teach the removal of a cancer specimen taken from a human cancer patient for determining drug samples having the highest cancer cell pharmacosensitivity (line 53 of col. 4 continues to line13 of col. 5), and that bladder cancer, breast cancer, colon carcinoma, non-small cell lung cancer, pancreatic cancer, liver cancer, prostatic carcinoma, acute myeloid leukemia, glioblastoma, osteogenic sarcaoma, ovarian carcinoma and others have all responded to the multidrug treatment (col. 11, lines 13-23). Medenica et al. also teach that the multidrug regimen may be administered by any of the methods known in the art, such as intravenous administration or even oral administration, particularly locoregional administration (locoregional intra-arterial infusion) or perfusion of chemotherapy to enhance the delivery of drug to the tumor due to its small blood supply (see the section titled "Administration of the Regimen", particularly col. 27, first full paragraph).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify the method taught by Urban et al. by using the specific recited chemotherapeutic drugs taught by Medenica et al. **in conjunction** with

a thiazolidinedione compound (e.g., troglitazone, pioglitazone and rosiglitazone) to inhibit the growth or killing tumor cells; particularly via locoregional intra-arterial infusion or perfusion administration of the pharmaceutical composition for treating a cancer patient.

One of ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Urban et al. the utilization of chemotherapeutic agents such as those taught by Medenica et al. **in conjunction** with the use of troglitazone or a thiazolidinedione compound increases the likelihood of curing a cancer patient. Additionally, Medenica et al. specifically teach that it is known that a chemotherapeutic treatment regimen utilizing several drugs may be more effective than the best single drug, particularly a degree of potentiation exists between the agents in their efficacy against tumor cells to a greater extent than normal cells (col. 2; lines 42-55), and that the multidrug regimen has low toxicity insofar as ineffective chemotherapeutic agents are eliminated from the regimen (col. 5, lines 35-38). Furthermore, one of ordinary skilled artisan would have been motivated to administer the pharmaceutical composition into a cancer patient via locoregional intra-arterial infusion or perfusion to enhance the delivery of drug(s) to the tumor due to its small blood supply as taught by Medenica et al. (see the section titled "Administration of the Regimen", particularly col. 27, first full paragraph). One of ordinary skilled artisan would also have been motivated to resect the tumor to decrease tumor burden in the patient or for obtaining a tumor specimen for determining chemotherapeutic drug samples having

the highest cancer cell pharmacosensitivity as taught by Medenica et al. (line 53 of col. 4 continues to line13 of col. 5).

One of ordinary skilled artisan would have a reasonable expectation of success because Urban et al. clearly teach that therapeutic levels of troglitazone or thiazonlidinedione compound can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9); and that even with human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Additionally, bladder cancer, breast cancer, colon carcinoma, non-small cell lung cancer, pancreatic cancer, liver cancer, prostatic carcinoma, acute myeloid leukemia, glioblastoma, osteogenic sarcaoma, ovarian carcinoma and others have all responded to the multidrug chemotherapeutic treatment taught by Medenica et al. (col. 11, lines 13-23).

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in amendment filed on 7/28/2003 in Paper No. 20 (pages 6-8) have been fully considered, but they are respectfully not found persuasive.

Once again, Applicants argue that Urban et al. does not teach any method of treatment that includes contacting the cancer cell with a thiazolidinedione compound

and a chemotherapeutic drug or irradiation in amounts effective to inhibit the growth of the cancer cell. Applicants further argue that a single vague statement by Urban et al. is not sufficient to teach a method using a chemotherapeutic drug or type of radiation in combination with a thiazolidinedione, and particularly in an area of unpredictability the general statement provided by Urban et al. would not lead one of ordinary skill in the art to conclude that the combination therapy would be successful with a reasonable expectation of success. The likelihood of antagonism or lack of additivity between components would be as likely as additive or synergistic effects.

The above arguments are found to be unpersuasive for the same reasons already set forth in the response to Applicants' arguments on the rejection of claims 1-10, 15-16, 27-28, 33-35, 39-42 and 46 above. Furthermore, it is noted that at the effective filing date of the present application, it was well known in the art a chemotherapeutic treatment regimen utilizing several drugs may be more effective than the best single drug, particularly a degree of **potentiation** exists between the agents in their efficacy against tumor cells to a greater extent than normal cells (col. 2; lines 42-55), and that **the multidrug regimen has low toxicity** insofar as ineffective chemotherapeutic agents are eliminated from the regimen (col. 5, lines 35-38) as evidenced by the teachings of Medenica et al.

Claims 1, 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Medenica et al. (U.S. Patent No. 5,736,129) as applied to claims 1, 16-25, 28-29

and 36-38 above, and further in view of Jin et al. (U.S. Patent No. 6,251,871 with the effective filing date of 7/17/1995) for the same reasons already set forth in the previous Office Action in Paper No. 19 (pages 9-10).

The combined teachings of Urban et al. and Medenica et al. have been discussed and applied above. However, none of the references teaches explicitly a step of further contacting the cancer cell with a therapeutic polynucleotide as recited in claim 32.

However, at the effective filing date of the present application Jin et al. already teach a method for inhibiting tumor growth (e.g., lung cancer tumor, bladder cancer tumor, a glioma, a melanoma, a head and neck cancer tumor) in a mammal by direct intratumoral administration of a recombinant vector encoding a p16 gene product (see abstract and claims). Additionally, Jin et al. teach that the p16 replacement therapy could be used **in conjunction** with chemo or radiotherapeutic intervention to improve the efficacy of chemo- and radiotherapy (see col. 19, lines 46-56; and section E on cols. 19-22). Moreover, Jin et al. teach gene therapies involving polynucleotides of p21, Rb, APC, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, ras, myc, neu, raf, erb, src, fms, jun, trk, ret, gsp, hst, bcl and abl can also be used (line 66 of col. 21 continues to line 7 of col. 22).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to further modify the combined method taught by Urban et al. and Medenica et al. by further contacting the cancer cell with a polynucleotide of

p16 or other therapeutic polynucleotides taught by Jin et al. for further inhibiting the growth or further killing tumor cells.

One of ordinary skilled artisan would have been motivated to further carry out the above modification to increase the efficacy of tumor cell killing or cancer growth inhibition as clearly taught by Jin et al.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in amendment filed on 7/28/2003 in Paper No. 20 (pages 8-9) have been fully considered, but they are respectfully not found persuasive.

Applicants provided the same lines of arguments as those presented in the response to the rejection of claims 1, 16-25, 28-29 and 36-38 above, and they are found unpersuasive for the same reasons set forth above.

Claims 1, 28 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Roth et al. (U.S. Patent No. 5,747,469) for the same reasons already set forth in the previous Office Action in Paper No. 19 (pages 10-13).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of

climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency

of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

Urban et al. do not teach explicitly the type of radiation utilized in combination with the troglitazone therapy for inhibiting the growth of a cancer cell.

However, at the effective filing date of the present application Roth et al. already disclose a method of killing cancerous cells using a tumor suppressor gene, p53 in a recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent (DNA damaging agent also encompasses chemotherapeutic agents such as 5FU, etoposide, camptothecin, mitomycin C, cisplastin) in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify the method taught by Urban et al. by using the specific recited irradiation taught by Roth et al. **in conjunction** with a thiazolidinedione compound (e.g., troglitazone, pioglitazone and rosiglitazone) to inhibit the growth or killing tumor cells.

One of ordinary skilled artisan would have been motivated to carry out the above modification to increase the efficacy of tumor cell killing or cancer growth inhibition. Urban et al. clearly teach that the use of troglitazone therapy **in conjunction** with other

chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment because of the increased likelihood of curing the patient.

One of ordinary skilled artisan would have a reasonable expectation of success because Urban et al. clearly teach that therapeutic levels of troglitazone or thiazonlidinedione compound can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9); and that even with human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Additionally, Roth et al. have already shown successfully the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent (DNA damaging agent also encompasses chemotherapeutic agents such as 5FU, etoposide, camptothecin, mitomycin C, cisplastin) in combination with p53 gene transfer for treating cancer.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in amendment filed on 7/28/2003 in Paper No. 20 (page 9) have been fully considered, but they are respectfully not found persuasive.

Applicants once again argue that the Roth reference has no bearing on the expectation of success of methods using thiazolidinedione in combination with other

chemotherapeutic drugs, irradiation, and or gene therapy, and that the analogy between thiazolidinedione and a gene therapy is simply not supported, particularly in light of the deficiencies of the Urban et al. reference. Applicants further argue that the combination of references has no basis for one of ordinary skill to have a reasonable expectation that thiazolidenedione in combination with other chemotherapy agents would be successful.

Urban clearly teach the essential concept of using troglitazone (as well as related thiazolidinedione compounds such as pioglitazone and BRL49653) therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery for the treatment of cancer. At the effective filing date of the present application, thiazolidinedione compounds were successfully used to kill tumor cells as evidenced by the teachings of Urban et al. (both U.S. Patent Nos. 5,814,647 and 6,207,690), Mueller et al., Brockman et al., Elstner et al., Kubota et al., and Tontonoz et al. as already discussed above. Additionally, chemotherapeutic agents, radiation or surgery were routinely used in cancer treatment at the effective filing date of the present application as evidenced by the teachings of Medenica et al., Jin et al. and Roth et al., for examples. Furthermore, it was also well known in the art a chemotherapeutic treatment regimen utilizing several drugs may be more effective than the best single drug, particularly a degree of **potentiation** exists between the agents in their efficacy against tumor cells to a greater extent than normal cells, and that **the multidrug regimen has low toxicity** insofar as ineffective chemotherapeutic agents are eliminated from the regimen. Particularly, Roth et al. have already shown successfully the use of gamma-irradiation, X-rays, UV-

irradiation or microwaves as a DNA damaging agent (DNA damaging agent also encompasses chemotherapeutic agents such as 5FU, etoposide, camptothecin, mitomycin C, cisplastin) in combination with p53 gene transfer for treating cancer. Therefore, one of ordinary skilled artisan would have a reasonable expectation of success to carry the presently claimed invention.

Claims 1, 9, 11-14, 40 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) in view of Pitot (In Fundamentals of Oncology, 3rd Edition, pages 29-32, 1986) for the same reasons already set forth in the previous Office Action in Paper No. 19 (pages 13-16).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of climacteric symptoms and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). Urban et al. teach "Studies show that troglitazone is a ligand for the orphan nuclear receptor PPARγ. Translocation of this transcription factor in the nucleus of cells at sufficient rates inhibits transcription and reduces progesterone production in normal granulosa cells without a loss of viability. However, this inhibition of transcription in rapidly dividing cancer cells expressing receptor PPARγ results in the loss of cell viability and inhibition of cell growth." (col. 3, lines 23-30). A type of cancer that is likely

to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy **in conjunction** with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Urban et al. also demonstrated that human breast cancer MCF-7 cells which do not express PPARγ have reduced cell viability at high concentrations of troglitazone (see example 6 and Fig. 13). Urban et al. further teach for preparing pharmaceutical compositions, pharmaceutically acceptable carriers can be either solid (e.g., powders, tablets, pills, suppositories) or liquid (e.g., solutions, suspensions, emulsions); and that oral administration and/or parenteral injection of the compositions can be used (see col. 19-20). The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg, preferably 0.5 mg to 100 mg according to particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents (col. 20, lines 8-18).

Urban et al. do not teach explicitly the cancer cell is a bone cancer cell, osteosarcoma cell, precursor of osteosarcoma cell, or ovarian cancer cell.

However, at the effective filing date of the present application, Pitot teaches that osteoma (benign bone cancer or precursor of osteosarcoma) and osteogenic sarcoma (malignant form or osteosarcoma) are derived from the mesodermal (mesenchymal) embryonic germ layer, and therefore they belongs to mesenchymal tumors (page 31, bottom of the first full paragraph and Table 2.1). Additionally, Pitot teaches that granulose cell tumor is a benign cancer of the ovary (see bottom of Table 2.1).

Accordingly, it would have been obvious for an ordinary skilled artisan to utilize troglitazone or thiazolidinedione compound in conjunction with other chemotherapeutic agents, radiation, or surgery to inhibit the growth of the recited cancer cells because bone cancer cells, precursors of osteosarcoma and osteosarcoma are classified as mesenchymal tumors as taught by Pitot. Furthermore, granulosa cell tumor is a benign neoplasm of ovary, whose growth and cell viability are inhibited by the action of troglitazone that has no effect on normal granulosa cells.

One of ordinary skilled artisan would have been motivated to carry out the above modification because Urban et al. clearly teach that troglitazone and related thiazolidinedione derivatives are useful for treating a broad range of mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma (**kidney**), rhabdomyosarcomas, fibrosarcomas, retinoblastoma, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22).

One of ordinary skilled artisan would also have a reasonable expectation of success because even with human breast cancer MCF-7 cells which do not express PPARγ decreased tumor cell viability at high concentrations of troglitazone was still obtained (see example 6 and Fig. 13).

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in amendment filed on 7/28/2003 in Paper No. 20 (pages 9-10) have been fully considered, but they are respectfully not found persuasive.

Applicants argue mainly that the Pilot reference does not remedy the deficiency of the Urban et al. reference since Urban et al. does not provide an enabling disclosure and as one of ordinary skill in the art would not have a reasonable expectation the teachings of Urban et al. would succeed with regard to a combination therapy.

Applicants' basic argument on the issue of non-enablement for the Urban et al. reference is respectfully found to be unpersuasive for the same reasons already set forth in Examiner's response to Applicants' arguments on the same issue in the above rejections.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER